

## Sickle cell disease and malaria

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**Abstract** Malaria is most common infectious disease spread by female Anopheles mosquitoes especially in tropical and subtropical areas of the world. It is reported by WHO as a 4th leading cause of death in children across the developing countries. Unfortunately no vaccine is currently available. Sickle cell trait (HbAS) patients provide some resistance for malaria over normal persons (HbAA) or their homozygous state (HbSS) due to various reasons.

**Keywords** Falciparum malaria · Sickle cell trait · Sickle cell disease

### Introduction

Malaria is one of the most common infectious diseases and an enormous public-health problem. It is a vector-borne disease spread by mosquitoes and widespread in tropical and subtropical regions. The most serious forms of the disease are caused by *Plasmodium falciparum* and *Plasmodium vivax*. It is a global problem and according to WHO report 2005 [1], it is 4th leading cause of deaths in children in many developing countries. According to reports there are 8,53,000 deaths due to malaria per year (8% of all deaths in this age group). According to the report:

- Some 3.2 billion people lived in areas at risk of malaria transmission in 107 countries and territories at the end of 2004.
- Between 350 and 500 million clinical episodes of malaria occur every year.
- At least one million deaths occur every year due to malaria.
- About 60% of the cases of malaria worldwide and more than 80% of the malaria deaths worldwide occur in Africa south of the Sahara. *Plasmodium falciparum* causes 18% deaths in children under 5 years of age.
- Malaria is also major cause of anemia in children and pregnant women.
- Pattern of malaria transmission vary between region and even within the countries

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India is also at high risk of malaria as 95% population of India live in malaria risk zone. Malaria transmission occurs almost in all areas of India except the parts which are 1800 meter high above sea level. About 90% malaria is unstable in India with relative low incidence with a risk of increase of

epidemic for every 7 to 10 or more years, this depends upon the immune status of population and breeding potential of mosquitoes. The incidence of malaria is maintained between 2 and 2.5 million annually for the last 10 years despite the increasing population at a rate of 2.1% annually [1].

Malaria parasites are transmitted by female Anopheles mosquitoes. The parasites multiply within red blood cells, causing symptoms that include symptoms of anemia (light headedness, shortness of breath, tachycardia etc.), as well as other general symptoms such as fever, chills, nausea, flu-like illness, and in severe cases, coma and death. Malaria transmission can be reduced by preventing mosquito bites by using insecticide-treated bed nets and insect repellents or by mosquito control by spraying insecticides inside houses, drains, ponds and pits where waterlogged and mosquitoes lay their eggs.

Unfortunately, no vaccine is currently available for malaria. Instead preventative drugs must be taken continuously to reduce the risk of infection. These prophylactic drug treatments are simply too expensive for most people living in endemic areas. Malaria infections are treated through the use of antimalarial drugs, such as chloroquine or pyrimethamine, although drug resistance is increasingly common.

### **Malaria defense and sickle cell**

There is significant evidence that sickle hemoglobin provides the changes in the hemoglobin molecule that impairs malaria growth and development. It is seen that the geographical distribution of sickle hemoglobin gene and distribution of malaria in Africa virtually overlap. It is also seen that peoples indigenous to the highland regions of the continent do not display the high expression of the sickle hemoglobin gene like their lowland neighbors in the malaria belts. Malaria does not occur in the cooler and drier climates of the highlands in the tropical and subtropical regions of the world. Neither does the gene for sickle hemoglobin.

Ringelmann et al reported that sickle trait (HbAS) provides a survival advantage over people with normal hemoglobin (HbAA) as well as people with sickle cell disease (HbSS) in regions where malaria is endemic. Sick cell trait provides neither absolute protection nor invulnerability to the disease. Rather, people (and particularly children) infected with *P. falciparum* are more likely to survive the acute illness if they have sickle cell trait. Therefore, the people with sickle cell trait are more likely to reach reproductive age and pass their genes on to the next generation [2]. Willcox et al also reported similar conclusion in their studies [3].

The genetic selective scenario in which a heterozygote for two alleles of a gene has an advantage over either of the homozygous states is called “balanced polymorphism”. Malaria has been invoked, as a force for the selection of human genetic polymorphisms. There is enough evidence that genome-shaping interactions are found in the geographic and ethnic distributions between malaria and of the hemoglobinopathies, blood group antigens, thalassemias, red cell membrane molecules, human lymphocyte antigen (HLA) classes, and cytokines [4]. In another study genetic polymorphism was studied between TNF alpha promoter gene and sickle cell trait and it was found that there were no differences in malariometric indices between infants with the normal TNF alpha promoter gene and those who were heterozygous for this trait. Infants who were heterozygous for the TNF alpha promoter gene had fewer febrile episodes when they were free of parasites. Whereas on the other hand, infants homozygous for the TNF alpha promoter allele had a much higher incidence of fever, irrespective of parasitaemia. Similar conclusion was also noted in infant with sickle cell trait as they have low parasite density than that of homozygous sickle cell disease [5]. It is a common misstatement that malaria selects for sickle cell disease, is not true. A person with sickle cell disease is at an extreme survival disadvantage because of the negative effects of the disease process. This means that a negative selection exists for sickle cell disease. Sick cell trait is the genetic condition selected for in regions of endemic malaria.

The mechanism by which sickle cell trait imparts resistance to malaria is unknown. There are a number of factors which involve in this process and contribute and have varying degrees to the defense against malaria.

Red cells of patients of sickle cell trait, when infected with the *P. falciparum* parasite, deform, most probably because the parasite reduces the oxygen tension within the erythrocytes to very low levels as it carries out its metabolism. Deformed sickle trait red cell when passes through splenic sinusoids sequestered out by the phagocytes [6]. Similar result was also obtained by Kodjo et al where in vitro experiment showed increased phagocytosis of ring parasitized RBCs in HbAS individual by mononuclear phagocytic system of spleen whereas trophozoite-parasitized normal RBC and RBC in HbAS were phagocytosed at equal pace. They concluded that ring parasitized RBC in sickle cell trait patients was predominantly complement mediated and very similar to phagocytosis of senescent or damaged normal RBCs. It was also concluded that the phagocytosis of ring parasitized red cells by monocytes have advantages in various ways, firstly it reduces parasite growth and density, secondly phagocytosed ring parasitized red cells digest rapidly by monocytes and process is repeat-

ed without loss of function whereas more mature form of parasite actively phagocytosed and severely affect the function of monocyte [7]. In another study in vitro experiment showed that sickle trait red cells infected with *P.falciparum* malaria sickled much more readily than uninfected cells under low oxygen tension [8]. Since sickle cells are removed from the circulation and destroyed in the reticuloendothelial system, it reduces the parasite burden in people with sickle trait. These people are more likely to survive acute malarial infections.

It was further highlighted in another study that malaria parasites could be killed directly in sickle red cells. When parasites cultured in sickle trait red cells and incubated at low oxygen tension, it died [9]. Ultra structural studies showed extensive vacuole formation in *P.falciparum* parasites in sickle trait red cells when incubated at low oxygen tension, suggest that there is some metabolic damage to the parasites [10].

Other investigations show that there is oxygen radical formation in sickle trait erythrocytes and it retards growth and even kills the *P.falciparum* parasite. There is more production of super oxides ( $O_2^-$ ) and hydrogen peroxide ( $H_2O_2$ ) in sickle trait red cell than the normal erythrocyte [11].

There is formation of membrane associated hemin in homozygous hemoglobin S red cell which can oxidize membrane lipid and protein. However sickle trait red cell produce little hemin. But infected sickle trait red cells owing to formation of sickle polymer due to low oxygen tension and due to parasite metabolism produce enough hemin to damage the parasites [12, 13].

Immune system also plays an important role in attack of *P.falciparum*. Maternal antibodies passed to fetus provide protection from malaria for first few months of life. Thereafter toddler's immune system provides protection. Many epidemiological studies conducted in endemic areas show that antibody titer of *P.falciparum* are lower in children in sickle cell trait than in normal children. It is speculated low level of titer might reflect a low parasite burden in children with sickle trait due to clearance of infected red cells. In contrast children suffering with sickle cell disease have high fatality rate when infected with *P.falciparum* parasites [14, 15, 16].

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